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The prevalence, impact, and cost of multimorbidity in a cohort of people with chronic pain in Ireland: Study protocol

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Abstract

Introduction: Multimorbidity (MM) refers to the coexistence of two or more conditions within one person, where no one condition is considered primary. As populations' age and health care provision improves, MM is becoming increasingly common and poses a challenge to the single morbidity approach to illness management, usually adopted by healthcare systems. Indeed, recent research has shown that 66.2 % of the people in primary care in Ireland are living with MM. Health care utilisation and cost is significantly associated with MM, and additional chronic conditions lead to exponential increases in service usage and financial costs, and decreases in physical and mental well-being. Certain conditions, for example chronic pain, are highly correlated with MM. This study aims to assess the extent, profile, impact, and cost of MM among Irish adults with chronic pain.

Methods and analysis: Using cluster sampling, participants aged 18 and over will be recruited from Irish pain clinics and sent an information package and questionnaire asking them to participate in our study at three time points, 1 year apart. The questionnaire will include our specially developed checklist to assess the prevalence and impact of MM, along with validated measures of quality of life, pain, depression and anxiety, and illness perception. Economic data will also be collected, including direct and indirect costs.

Ethics and dissemination: Ethical approval has been granted by the Research Ethics Committee of the National University of Ireland, Galway. Dissemination of results will be via journal articles and conference presentations.

Main strength and weakness

Strength:

- The research study aims, to account for the prevalence and cost of multimorbidity in people living with chronic pain' are novel and would provide useful information for both the applied and research communities.

Weakness:

- Given the cohort of participants, the sample type, may arguably, be considered not entirely representative of all people living with chronic pain.

The guidelines for chronic disease management have traditionally taken a single disease approach,[1] which presents a challenge for patients who have multiple, sometimes discordant chronic conditions. As such, it has been argued that a single-morbidity approach in the context of multiple health conditions typically leads to inadequate disease management. [1] Thus, there has been a call for a more 'holistic' consideration of the patient and a disease management approach that focuses on *multimorbidity*.[1,2] Multimorbidity (MM) refers to the coexistence of two or more conditions within one person, where no one condition takes precedence over another.[3] Despite the increasing interest of healthcare practitioners in the area of MM, Marengoni et al,[4] note that there remains "a remarkable gap between the harmful impact of multimorbidity at the individual and societal level and the amount of scientific and clinical research devoted to this topic" (p.435).

Prevalence of Multimorbidity

Prevalence estimates of MM in the literature vary from 17% to over 90%.[5] However, in their Public Health Review, Boyd and Fortin [3] concluded that approximately one out of every four adults has two or more chronic conditions, and that half of all older adults have three or more chronic conditions. From an Irish perspective, relatively little research on the prevalence of MM has been conducted; however, available figures show that between 27% [6] and 66.2% [7] of the population have two or more chronic conditions. While there is some uncertainty regarding the exact prevalence rates of MM, it is clear that MM is becoming increasingly more common.[5] Contributing factors to the increase in MM include, ageing populations, better medical treatments, lifestyle factors, and the increased prevalence of certain diseases in particular populations.[5, 8]

Impact of MM: challenges for patients and health practitioners

The occurrence of MM has significant social, psychological, economic, and physical implications for a person, creating a variety of management and treatment challenges. [3] For instance, different conditions require different and sometimes incompatible treatment solutions and as a result, multiple coexisting conditions can complicate medical treatment and affect long term recovery. Indeed, MM can contribute to a person becoming increasingly ill compared to another person with any one of the same index diseases but without MM, and it has also been linked to higher rates of postoperative complications.[9] Research on the impact of MM shows that it causes a decline in physical and mental functioning, is correlated

with mental health issues, negatively influences quality of life, ability to work and employability, and is associated with increased mortality risk, as well as longer hospital stays and higher levels of health care usage.[3, 4, 9, 10]

MM and Chronic Pain

Chronic pain (CP) is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described by the patient in terms of such damage" that persists for a period in excess of 3 months. [11] CP is a major public health problem that can have debilitating physical, emotional, psychological, and financial consequences for those individuals living with it (see Azevedo, et al., 2012; Kroenke et al., 2013; Raftery et al., 2011). Prevalence estimates for CP vary across studies and countries; [12-16] one recent study found that 35.5% of the Irish population were living with CP. [14]

CP is highly correlated with MM, and is consistently identified as one of the most common conditions in those identified as having MM.[5] For example, in one Canadian study examining the prevalence of disease-combinations, sixteen common disease pairs were identified, with CP appearing in six of the combinations. Further, from the five most common disease triads identified in the same study, CP was involved in three of these combinations.[5] As Boyd and Fortin [3] note, if a person has one chronic condition they are quite likely to also have another. Considering that over a third of the Irish population are reported to have CP, and that CP is highly correlated with MM, it is important that research examines the prevalence and the relationship between the two more closely. While previous studies have examined the prevalence of MM in Irish samples, [7] no previous Irish study has examined the prevalence of MM in a population of people with CP.

Aims of the current research:

1. To determine the prevalence, impact, and cost of multimorbidity in a cohort of people in Ireland who live with chronic pain.
2. To identify the nature and profile of multimorbidity in which chronic pain is a central feature.
3. To develop a predictive model of multimorbid disability in a population of people with chronic pain.
4. To chart the developmental trajectory of multimorbidity in a sample of people with chronic pain.

Method

Design:

A prospective cohort study with three time points (1 year apart) assessing the prevalence of multimorbidity in a cohort of people with chronic pain will be employed.

Ethical Approval:

Ethical approval was granted by NUI Galway's Research Ethics Committee on 15 July 2015 (Reference number: 15/JULY/01).

Data Collection and Sample Size:

Inclusion criteria:

All participants of this study must be over 18 years of age and experiencing chronic non-cancer pain (according to the IASP definition). Individuals with terminal illness, severe mental illness or cognitive impairment that would prevent adequate understanding and participation in the study will be excluded.

Recruitment:

Recruitment will be carried out through Irish pain clinics. Staff in the pain clinics will inform patients of the study. Participants will be identified via the patient records from each of the 16 Pain Clinics in the Republic of Ireland; a list of patients who have visited each clinic over the previous 18 months will be requested, each patient will be given an identifier, and Stata 13.1 [17] will be used to randomly select 150 participants from each clinic. These participants will be posted the survey packs containing the study information sheets, consent forms, multimorbidity checklist, and questionnaires by the research team. The participants will be directed to post their completed packs to the NUI Galway Centre for Pain Research using a stamped addressed envelope provided. In addition, the pack will contain a link to our website where the participants will able to complete the survey online should they prefer this method to the postal system.

Sample size:

Sample size was calculated using the equation proposed for prevalence research by Naing Winn and Rush (2006).[18] To calculate the sample size for a prevalence study, the expected

prevalence is required. Based on previous research,[6, 7, 14, 19] the expected prevalence of MM in a population of people with CP is approximately between 22% and 54%. Nicholl [20] notes that if there is a doubt about the prevalence total in a given population, researchers should err toward assuming a 50% prevalence rate as it will yield a larger sample size. Therefore, using Naing et al's [18] equation and predicting that 50% of our sample may exhibit multimorbidity, confidence intervals set at .95, and the degree of precision (*d*) = .05 produced a sample size of 384. Using a predicted response rate of 40%, based on previous Irish prevalence research in the area of chronic pain, the sample size was calculated as 960. As we are sampling from Irish pain clinics, the design effect of using a cluster randomised trial must be taken into account, however, we were unable to identify a suitable intra-cluster correlation coefficient. Therefore, as demonstrated in a similar study on prevalence, [14] a median value of 0.01 was used. Adjusting for this, with an average of 150 patients per cluster, gives a design effect of 2.49 and a sample of 2391. A target sample of 2,400 will be recruited; 150 patients from each of the 16 Irish pain clinics.

Measures:

Sociodemographic and health information

Participants will be asked to supply details regarding age, gender, relationship status, highest educational attainment, occupational status (working full-time, working part-time, retired, unemployed, occupied with home duties, or other) and their occupation, to determine socioeconomic status (SES), as well as duration of chronic conditions, site(s) of chronic pain, and cause of chronic pain. Some details about previous and current medical and alternative treatments will also be collected.

Primary Measure:

The main focus of this study is to assess the point prevalence of multimorbidity in a cohort of people with chronic pain in Ireland. To that end, a specific disease count measure was developed.

Background to current MM Checklist

As Diederichs, Berger, and Bartels [10] highlight, there is no 'gold standard' measure of multimorbidity. Several measures of MM exist and have been developed for a variety of reasons, including different definitions of MM, different purposes for measuring MM, different required or available resources for data collection, and the type of data available.[7,

21] Moreover, there are no definitive criteria for the selection of chronic conditions that qualify for multimorbidity and therefore, no standardised list of the number and type of diseases to be included in a multimorbidity measure.[10] In a review of the literature, de Groot, Beckerman, Lankhorst, and Bauter [22] found that there were thirteen common measures of MM: twelve of these were disease indexes and one was a disease count.

Researchers that are interested in tallying the number of conditions that occur in patients as an outcome, or those examining the prevalence of MM, primarily use disease counts (e.g., Bayliss et al.[21]). To develop a disease count measure, researchers typically select and include the most common conditions found in the targeted population. For example, Bayliss, et al. [21] reviewed the literature and selected the 25 most common chronic conditions for a US sample to include in their measure. They developed a subjective scale or disease count, where participants marked which diseases they had and then rated them in terms of severity (i.e., how much each one affected their daily functioning).

Although different viewpoints exist regarding what conditions to include and how they should be selected for a MM disease count measure, guidelines [21, 23] have been proposed to address these issues, which are based on work yielded from systematic reviews in the area.

Guidelines for developing an MM checklist

Fortin et al [23] proposed an operational definition of MM, whereby two or more diseases should be present in an individual and meet the diagnostic criteria for two separate areas of the Cumulative Illness Rating Scale (CIRS).[24] The CIRS is a measure that weights the severity of multimorbidity. It is divided into sections based on 14 different organ systems. These organ systems are as follows: 1. Cardiac, 2. Vascular, 3. Hematopoietic, 4. Respiratory, 5. Eyes, Ears, Nose, Throat and Larynx, 6. Upper GI, 7. Lower GI, 8. Hepatic, 9. Renal, 10. Genitourinary, 11. Musculoskeletal, 12. Neurological, 13. Endocrine/ Metabolic and Breast, and 14. Psychiatric. For a person to be considered to have a diagnosis of multimorbidity, chronic disease must be present in at least two different sections or organ systems. However, it is not necessary for a disease count to list either all conditions or all CIRS body systems. Fortin et al [23] recommend a minimum of seven conditions and argued that any list of conditions included in a MM prevalence study, should reflect the most common conditions in the population to be studied.

Process for developing the current MM checklist

In line with Fortin et al's [23] recommendations, the conditions included in the current disease count questionnaire were obtained from two large scale national reports on the Irish population more widely [25, 26] and four Irish research studies that had investigated the prevalence of multimorbidity and had compiled lists of conditions to examine.[6, 19, 26, 27] To ensure the list of conditions met international best practice recommendations, [21, 23] in terms of which conditions to include in an MM disease count list, we then combined our study with one international study that examined MM in people living with CP.[5] We also examined two of the most recent systematic reviews, which outline the most common conditions included in MM studies and contain recommendations for the type of conditions to be included in MM checklists.[10, 28] Following this, two health care practitioners were consulted and provided feedback, on which conditions to include, and one clinician, who is an expert in chronic pain, reviewed the entire MM checklist. From this review process, the three additional categories of conditions included were, as follows renal disorders, hepatic disorders, and headache disorders. Subsequently, we collapsed the conditions from this developmental process with respect to the CIRS organ system domains and removed any duplicate conditions, leaving us a total of 34 conditions across 10 organ domains (see Table 1). We also added category options (e.g. "Other cardiac conditions") to ensure that useful data could be collected on conditions that didn't appear on the list, as well as a final "Any other condition not listed" category.

INSERT TABLE 1 HERE

Structure of MM checklist and operational definition of MM

Based on Fortin et al's [29] suggestion, a condition will be deemed suitable for inclusion as a multimorbidity when it meets one or both of the following criteria; a formal diagnosis has been provided by a doctor, and/ or a person is receiving prescribed medication for the particular condition. To ensure that participants understand what each condition is, a lay definition derived from a medical definition for each condition (see U.S. National Library of Medicine MeSH database [30]) will be provided (see Appendix A). Furthermore, similar to Bayliss et al,[21] who created a subjective survey disease count measure of MM, the current measure will include a rating scale (from 1 to 5; 1 being least impactful and 5 being most impactful) measuring the impact that each condition has on their daily functioning. The inclusion of this rating scale will enable the research to identify which chronic conditions

have more of an impact on daily functioning and indeed, which disease combinations have more of a cumulative impact on daily functioning.

Secondary Measures

A number of secondary measures will be included to provide an accurate representation of the impact of MM and CP on participants. The measures outlined below were chosen to quantify the prevalence and impact of MM for people living with CP and were based on inclusion in previous chronic pain and multimorbidity prevalence research. [14]

Health Related Quality of Life

The Medical Outcomes Short Form-12 (SF-12) [31] will be used to assess health related quality of life. The SF-12 is a general measure of health-related quality of life that has been used and validated with European populations.[32] The SF-12 gathers information across 8 health domains; general health, physical functioning, emotional role limitation, physical role limitation, mental health, bodily pain, vitality, and social functioning. According to the norm-based method recommended by the test author, these items are scored to produce a Mental Component Summary (MCS) and Physical Component Summary (PCS) of health-related quality of life.[31] Lower scores on either of these scales are indicative of a lower quality of life. Irish population norms are available [33] and will be used for comparison to the present sample. The SF-12 has been used as a measure of health related quality of life previously within chronic pain research and multimorbidity research. [20, 34, 35]

Depression and anxiety

Depression will be measured using the PHQ-9. The PHQ-9 is a widely used and well validated measure of depression [13] and it has been used with people living with chronic conditions. [36] The PHQ-9 contains 9 items that relate to the DSM IV criteria for depression. The items are scored on a 4 point Likert scale ranging from 0 “not at all” to 3 “nearly every day”. The higher the score on the PHQ-9, the more symptom criteria a person meets. A cut-off score of above 10 indicates moderate depression and a score of above 15 indicates a clinical “case” of moderately severe depression.

Anxiety will be measured using the GAD-7. The GAD-7 is a validated and standardised measure of anxiety [37] and has been recommended for use in Chronic Pain studies.[38] The GAD-7 is a 7 item questionnaire that presents items relating to how often over the past couple of weeks a person has felt bothered by each of DSM IV symptom criteria

for generalized anxiety disorder. Items are scored on a 4 point Likert scale ranging from 0 "not at all" to 3 "nearly every day". A higher overall score represents greater symptom severity.

Pain severity and disability

Pain related severity and disability will be measured by the Chronic Pain Grade Questionnaire, [39] commonly used in pain research. The Chronic Pain Grade Questionnaire categorises pain severity into one of four grades based on two dimensions; intensity and disability depending on pain experiences in the previous 3-6 months. It contains 7 items which can be completed by self-report, and includes questions both about the pain itself and its impact on daily functioning.

Pain intensity and interference

Intensity of pain and the degree of interference in the participant's life will be measured by the Brief Pain Inventory, specifically the short form of the tool. [40] This includes 9 items, to be completed by self-report, and asks about pain both now and over time. Two scores are given: pain severity (out of 40) and pain interference (out of 70). Higher scores indicate greater pain severity and interference.

Multimorbidity Illness Perceptions Scale

The Multimorbidity Illness Perceptions Scale (MULTIPleS) [41] was developed to measure patient illness perceptions in the presence of multimorbidity. The MULTIPleS is a 22 item questionnaire. Each item has a Likert scale that runs from 0 to 3, where '0' indicates that a person 'strongly disagrees' with an item and '3' indicates that a person 'strongly agrees' with an item. Overall, the 22 items comprise five subscales; emotional representation, treatment burden, prioritising conditions, causal links, and activity limitations. The MULTIPleS is a relatively new scale so it has not yet been used as measure in clinical research. However, Gibbons et al [41] found that the scale provided a good fit to the Rasch model and demonstrated evidence of reliability and validity for each of the subscales.

Economic evaluation

The economic evaluation will be based on a number of questions relating to utilisation of healthcare services and financial costs to the participant (similar to Raftery, Ryan & Normand [42]). More specifically, we will examine costs that fall on the health and social care services

by recording hospitalisations (frequency and duration), outpatient appointments, Accident and Emergency appointments, types and amounts of benefits received per month, community services used (e.g., GP and home help), and medication type, dosage, and frequency. These services/products will be translated into unit cost data for Ireland and provide an estimate of the cost of MM where CP is a feature for the health service. Furthermore, we will calculate indirect costs incurred personally by each individual with MM and their family. These will include expenditure for treatments and medications not paid for by the state, and the travel and wait time costs associated with availing of health services. Opportunity costs will also be calculated by quantifying work absenteeism or reduced employment due to MM. To generate this data, information on wages will be collected, however, should collecting this information not be possible, we will extrapolate income from age, education, and work type.

Statistical Analyses

Graphical (e.g. box plots, labelled scatter-plots and case profiles plots) and numerical summaries (means, medians, standard deviations and interquartile ranges) will be provided for all variables. A chi-square (χ^2) test will be used to evaluate the relationship between gender and number of conditions. Odds Ratios will be calculated for risk factors of MM. Factors associated with MM will be analysed using univariate multiple regression and hierarchical regression will be employed to examine the relationships among the number and type of conditions and the outcome variables (i.e., depression, anxiety, QOL, illness perceptions, and severity of pain for example). All analyses will be conducted using SPSS version 22.

Data monitoring and management

This study will collect non-identifying, minimally invasive information and as such does not require a formal data monitoring committee. All information collected will be stored securely at the research site. Paper documents will be kept in locked cabinets, and electronic data will be stored on password-protected databases that can only be accessed by the research team.

Dissemination

Findings of the study will be disseminated in peer-reviewed publications following the data analysis. Researchers will also present the results at conferences. The research programme website will be regularly updated with news about the study to facilitate dissemination to the general public.

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Table 1: Source and Summary of Conditions included in the Multimorbidity Checklist

This table summarises the process of integrating previous multimorbidity studies and their listed conditions with the body system (CIRS domain) approach to develop the final list of conditions that appear in our multimorbidity tool (see the rightmost column). The asterisk denotes conditions included, as a result of advice from a healthcare practitioner.

CIRS Domain	Study and included conditions									**Included MM Checklist conditions**
	Teljeur et al 2013	Naughton et al 2006	Household Quarterly Report 2010	CARDI 2011/ Savva et al 2011 unpublished manuscript	TILDA 2011 Report: Fifty plus in Ireland	Diedrichs et al 2011 (systematic review)	Sinige et al 2013 (systematic review)	Agborsangaya et al 2012	Sinnott et al, 2015	
Cardiac	Heart disease	Hypertension/heart failure, Arrhythmias	Heart Attack, Heart Failure	Angina, Heart Attack	Cardiovascular disease (Angina, Heart attack, heart failure)	chronic ischemic heart disease, arrhythmia, insufficiency, infarction	Heart disease, heart failure, attack, angina (coronary artery disease)		Prior heart attack, angina, heart failure, aortic aneurysm, other cardiac disease, peripheral vascular disease,	**Angina, Arrhythmia, Heart Failure, Heart attack, other**
Vascular	hypertension	hypertension	Hypertension		hypertension	Hypertension	hypertension	Hypertension	Hypertension	**Hypertension**
Hematopoietic	High cholesterol, Hyperlipidaemia,	Hypercholesterolemia	High Cholesterol				Lipid metabolism disorders	High cholesterol		**High cholesterol**
Respiratory	Chest/lung disease, Asthma	Respiratory conditions		Asthma, COPD	Respiratory disease (e.g., bronchitis or emphysema)	COPD	COPD, Asthma		Asthma, bronchitis	**Asthma, Bronchitis, emphysema, COPD, other**
Eyes, ears, nose, throat and larynx		Glaucoma			Eye disease (e.g., glaucoma, age-related macular degeneration, cataracts)					**Glaucoma, other**
UPPER GI (esophagus, stomach, duodenum)							Gastrointestinal disease			**Gastrointestinal disease, Other GI conditions**
LOWER GI										

***Hepatic**										**Liver disease (e.g., Hepatitis)**
***Renal**										**Kidney disease (e.g., Chronic kidney disease)**
Genitourinary									Urinary incontinence	**Urinary incontinence, other**
Musculoskeletal	arthritis	Musculoskeletal conditions, Pagets/osteoporosis, Rheumatological conditions	Osteoporosis		Pain, arthritis, osteoporosis		Arthritis, osteoarthritis, osteoporosis, chronic back or neck disorder	Arthritis,	Chronic back pain, osteoarthritis, osteoporosis, rheumatoid arthritis	**Back pain or problem, neck pain or problem, osteoporosis, osteoarthritis, rheumatoid arthritis, other**
***Headache disorders**										**Headache disorder (e.g., Migraine, cluster headaches, tension headaches)**
Neurological		Parkinson's disease, dementia	Stroke	Stroke	Stroke/ TIA	Stroke	Dementia, cerebrovascular disease/ stroke		Stroke	**Stroke, TIA, Dementia, Other CNS conditions**
Endocrine/ metabolic and breast	Diabetes, hypothyroidism, obesity	Diabetes, thyroid disorders		Diabetes	Diabetes	Diabetes	Diabetes, Thyroid disease, obesity	Diabetes, obesity	Thyroid disease, diabetes	**Diabetes (Type 1), Diabetes (Type 2), Hypothyroidism, Obesity Other**
psychiatric	Depression	Psychiatric disorders, anxiety			Depression, anxiety	Depression	Depression	Depression/ anxiety	Anxiety, depression	**Depression, anxiety, other**
Other conditions:		Cancer		Cancer		Cancer	Cancer	Cancer	Cancer	**Any cancer in the past 5 years**
		Epilepsy, Gout, sleep disturbance						Sleep apnoea		**Epilepsy, Gout, Chronic sleep disturbance**

*CIRS = Cumulative Illness Rating Scale; MM = Multimorbidity

Appendix A: Included conditions

The table below describes the conditions included in our study in more detail, using the MeSH descriptions for each condition for clarity. Each condition also lists a lay description, which will be used for greater clarity in the final questionnaire.

Condition	MeSH Description	Lay Description
Angina	The symptom of paroxysmal pain consequent to MYOCARDIAL ISCHEMIA usually of distinctive character, location and radiation. It is thought to be provoked by a transient stressful situation during which the oxygen requirements of the MYOCARDIUM exceed that supplied by the CORONARY CIRCULATION.	Angina is chest pain or discomfort where your heart muscle does not get enough blood, which may feel like pressure or a squeezing pain in your chest, indigestion, or pain in your shoulders, arms, neck, jaw or back. There are three types of angina: stable, unstable and variant.
Arrhythmia	Any disturbances of the normal rhythmic beating of the heart or MYOCARDIAL CONTRACTION. Cardiac arrhythmias can be classified by the abnormalities in HEART RATE, disorders of electrical impulse generation, or impulse conduction.	Cardiac arrhythmia, also known as cardiac dysrhythmia or irregular heartbeat, is a group of conditions where the heartbeat is irregular, too fast, or too slow.
Heart Failure	A heterogeneous condition in which the heart is unable to pump out sufficient blood to meet the metabolic need of the body.	A condition which occurs when the heart is unable to pump sufficiently to meet the body's needs.
Heart Attack	NECROSIS of the MYOCARDIUM caused by an obstruction of the blood supply to the heart (CORONARY CIRCULATION).	A heart attack occurs when blood stops flowing to part of the heart causing damage to the heart muscle. Also known as myocardial infarction (MI) or acute myocardial infarction (AMI),
Other Cardio	Aneurysm, atherosclerosis, peripheral artery disease, pericardial disease, cardiomyopathy or other	
Hypertension	Persistently high systemic arterial BLOOD PRESSURE. Based on multiple readings (BLOOD PRESSURE DETERMINATION), hypertension is currently defined as when SYSTOLIC PRESSURE is consistently greater than 140 mm Hg or when DIASTOLIC PRESSURE is consistently 90 mm Hg or more.	Blood pressure is the force of blood pushing against the walls of the arteries as the heart pumps blood. Hypertension or high blood pressure refers to this pressure rising and remaining high.
High Cholesterol	A condition with abnormally high levels of CHOLESTEROL in the blood. It is defined as a cholesterol value exceeding the 95th percentile for the population.	The presence of high levels of cholesterol in the blood (also called hypercholesterolemia or dyslipidaemia).
Hepatic conditions	Liver disease, cirrhosis, hepatitis, other liver conditions or other	
Asthma	A form of bronchial disorder with three distinct components: airway hyper-responsiveness (RESPIRATORY HYPERSENSITIVITY), airway INFLAMMATION, and intermittent AIRWAY OBSTRUCTION. It is characterized by spasmodic contraction of airway smooth muscle, WHEEZING, and dyspnea (DYSPNEA, PAROXYSMAL).	A common chronic disease of the airways which obstructs normal breathing with wheezing and coughing.
Bronchitis	A subcategory of CHRONIC OBSTRUCTIVE PULMONARY DISEASE. The disease is characterized by hypersecretion of mucus accompanied by a chronic (more than 3 months in 2	Chronic bronchitis is defined as a cough that occurs every day with sputum production and that lasts for at least 3 months.

	consecutive years) productive cough. Infectious agents are a major cause of chronic bronchitis.	
Emphysema	Enlargement of air spaces distal to the TERMINAL BRONCHIOLES where gas-exchange normally takes place. Pulmonary emphysema can be classified by the location and distribution of the lesions.	An inflammatory response in the lungs resulting in narrowing of the small airways and breakdown of lung tissue
Chronic Obstructive Pulmonary Disease (COPD)	A disease of chronic diffuse irreversible airflow obstruction. Subcategories of COPD include CHRONIC BRONCHITIS and PULMONARY EMPHYSEMA. Enlargement of air spaces distal to the TERMINAL BRONCHIOLES where gas-exchange normally takes place. This is usually due to destruction of the alveolar wall. Pulmonary emphysema can be classified by the location and distribution of the lesions.	A type of obstructive lung disease characterized by chronically poor airflow
Other Respiratory	Pulmonary edema, embolism, obstructive sleep apnea, tuberculosis or other	
Glaucoma	An ocular disease, occurring in many forms, having as its primary characteristics an unstable or a sustained increase in the intraocular pressure which the eye cannot withstand without damage to its structure or impairment of its function.	A group of ocular (eye) disorders that result in optic nerve damage, often associated with increased fluid pressure in the eye
Other Eyes, Ears, Nose, and Throat	Hearing loss, tinnitus, meniere's disease, sinus conditions, obstructive sleep apnea, vocal cord disorders or other	
Gastrointestinal disease	Disease in any part of the GASTROINTESTINAL TRACT or the accessory organs (LIVER; BILIARY TRACT; PANCREAS).	Disease involving the gastrointestinal tract, namely the oesophagus, stomach, small intestine, large intestine and rectum, and the accessory organs of digestions, the liver (e.g., hepatitis), gallbladder, and pancreas (e.g., diabetes).
Other GI conditions	IBS, colitis, GERD or other	
Renal conditions	Kidney disease, renovascular disease, amyloidosis, lupus nephritis, or other	
Back Pain or Problem	Chronic pain located in the posterior regions of the THORAX; LUMBOSACRAL REGION; or the adjacent regions.	Pain felt in the back that usually originates from the muscles, nerves, bones, joints or other structures in the spine.
Neck pain or problem	Discomfort or more intense forms of pain that are localized to the cervical region. This term generally refers to pain in the posterior or lateral regions of the neck.	Pain felt in the neck
Other Pain Condition	Pain in any other location or a more general pain condition	
Osteoporosis	Reduction of bone mass without alteration in the composition of bone, leading to fractures. Primary osteoporosis can be of two major types: postmenopausal osteoporosis (OSTEOPOROSIS, POSTMENOPAUSAL) and age-related or senile osteoporosis.	A disease where decreased bone strength increases the risk of a broken bone
Osteoarthritis	A progressive, degenerative joint disease, the most common form of arthritis, especially in older persons.	Osteoarthritis (also known as degenerative arthritis, degenerative joint disease, or osteoarthrosis) is a type of joint disease that results from

		breakdown of joint cartilage and underlying bone
Rheumatoid arthritis	A chronic systemic disease, primarily of the joints, marked by inflammatory changes in the synovial membranes and articular structures, widespread fibrinoid degeneration of the collagen fibers in mesenchymal tissues, and by atrophy and rarefaction of bony structures.	A chronic, systemic inflammatory disorder that primarily affects joints
Other muskuloskeletal	Carpal tunnal syndrome, tendonitis, joint disorders, other bone/muscle/joint pain, repetitive strain injury or other	
Stroke	A group of pathological conditions characterized by sudden, non-convulsive loss of neurological function due to BRAIN ISCHEMIA or INTRACRANIAL HEMORRHAGES. Stroke is classified by the type of tissue NECROSIS, such as the anatomic location, vasculature involved, etiology, age of the affected individual, and hemorrhagic vs. non-hemorrhagic nature.	Stroke (also known as cerebrovascular accident (CVA), cerebrovascular insult (CVI), or brain attack) is when poor blood flow to the brain results in cell death. There are two main types of stroke: ischemic due to lack of blood flow and hemorrhagic due to bleeding.
TIA (Transient Ischaemic Attack)	Brief reversible episodes of focal, non-convulsive ischemic dysfunction of the brain having a duration of less than 24 hours, and usually less than one hour, caused by transient thrombotic or embolic blood vessel occlusion or stenosis	Often referred to as mini-strokes - A short, temporary episode of neurologic dysfunction caused by loss of blood flow.
Dementia	An acquired organic mental disorder with loss of intellectual abilities of sufficient severity to interfere with social or occupational functioning. The dysfunction is multifaceted and involves memory, behavior, personality, judgment, attention, spatial relations, language, abstract thought, and other executive functions. The intellectual decline is usually progressive, and initially spares the level of consciousness.	A broad category of brain diseases that cause a long term and often gradual decrease in the ability to think and remember such that a person's daily functioning is affected
Headache disorders	E.g. migraine, cluster headache, tension headaches	
Other CNS/Neuro conditions	Bell's palsy, dyskinesia, multiple sclerosis, motor speech disorders, Parkinson's, motor neurone disease or other	
Diabetes (Type 1),	A subtype of DIABETES MELLITUS that is characterized by INSULIN deficiency. It is manifested by the sudden onset of severe HYPERGLYCEMIA, rapid progression to DIABETIC KETOACIDOSIS, and DEATH unless treated with insulin. The disease may occur at any age, but is most common in childhood or adolescence.	Lack of insulin resulting from the autoimmune destruction of the insulin-producing cells in the pancreas which leads to increased blood and urine glucose, where administration of insulin is essential for survival
Diabetes (Type 2),	A subclass of DIABETES MELLITUS that is not INSULIN-responsive or dependent (NIDDM). It is characterized initially by INSULIN RESISTANCE and HYPERINSULINEMIA; and eventually by GLUCOSE INTOLERANCE; HYPERGLYCEMIA; and overt diabetes. Type II diabetes mellitus is no longer considered a disease exclusively found in adults. Patients seldom develop KETOSIS but often exhibit OBESITY.	A metabolic disorder that is characterized by high blood sugar in the context of insulin resistance and relative lack of insulin, initially managed by increasing exercise and dietary changes

Hypothyroidism	A syndrome that results from abnormally low secretion of THYROID HORMONES from the THYROID GLAND, leading to a decrease in BASAL METABOLIC RATE.	A common endocrine disorder in which the thyroid gland does not produce enough thyroid hormone. It can cause a number of symptoms, such as tiredness, poor ability to tolerate cold, and weight gain
Other Endocrine/Metabolic	Cushing's syndrome, cystic fibrosis, hyperthyroidism, PCOS, or other	
Depression	An affective disorder manifested by either a dysphoric mood or loss of interest or pleasure in usual activities. The mood disturbance is prominent and relatively persistent.	Clinical depression (also known as major depressive disorder (MDD), major depression, unipolar depression, or unipolar disorder; or as recurrent depression in the case of repeated episodes) is a mental disorder characterized by a pervasive and persistent low mood that is accompanied by low self-esteem and by a loss of interest or pleasure in normally enjoyable activities
Anxiety	Persistent and disabling ANXIETY. - Feeling or emotion of dread, apprehension, and impending disaster	Anxiety disorders are a group of mental disorders characterized by feelings of anxiety and fear
Other psychiatric	Eating disorders, obsessive compulsive disorders, schizophrenia, bipolar disorder, pervasive developmental disorder, substance abuse or other	
Any cancer in the past 5 years	New abnormal growth of tissue. Malignant neoplasms show a greater degree of anaplasia and have the properties of invasion and metastasis, compared to benign neoplasms.	Cancer, also known as a malignant tumour or malignant neoplasm, is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body
Epilepsy	A disorder characterized by recurrent episodes of paroxysmal brain dysfunction due to a sudden, disorderly, and excessive neuronal discharge. Epilepsy classification systems are generally based upon: (1) clinical features of the seizure episodes (e.g., motor seizure), (2) etiology (e.g., post-traumatic), (3) anatomic site of seizure origin (e.g., frontal lobe seizure), (4) tendency to spread to other structures in the brain, and (5) temporal patterns (e.g., nocturnal epilepsy).	A group of neurological disorders characterized by epileptic seizures. Epileptic seizures are episodes that can vary from brief and nearly undetectable to long periods of vigorous shaking
Gout	Hereditary metabolic disorder characterized by recurrent acute arthritis, hyperuricemia and deposition of sodium urate in and around the joints, sometimes with formation of uric acid calculi.	Usually characterized by recurrent attacks of acute inflammatory arthritis—a red, tender, hot, swollen joint.
Genitourinary conditions	Urinary incontinence, urinary frequency, chronic UTI, or other	
Sleep Disorder	Conditions characterized by disturbances of usual sleep patterns or behaviors. Sleep disorders may be divided into three major categories: DYSSOMNIAS (i.e. disorders characterized by insomnia or hypersomnia), PARASOMNIAS (abnormal sleep behaviors), and sleep disorders secondary to medical or psychiatric disorders	Sleep disorders are broadly classified into dyssomnias, parasomnias, circadian rhythm sleep disorders involving the timing of sleep, and other disorders including ones caused by medical or psychological conditions and sleeping sickness.
Obesity	To be determined by calculating BMI	
Any other conditions	Please list any other conditions that affect you but do not appear on this list:	

Author's contributions

BWS, LO'C, SH are involved in the design, delivery and evaluation of the trial and also drafted the manuscript. CPD, LC, JE and SO'H were involved in the editing of the manuscript and will be involved in the evaluation of the trial. BMcG contributed to the design of the intervention, supervises the study, and contributed to editing the manuscript.

Competing interests

The authors declare that they have no competing interests.

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The prevalence, impact, and cost of multimorbidity in a cohort of people with chronic pain in Ireland: Study protocol

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Abstract

Introduction: Multimorbidity (MM) refers to the coexistence of two or more chronic conditions within one person, where no one condition is considered primary. As populations' age and health care provision improves, MM is becoming increasingly common and poses a challenge to the single morbidity approach to illness management, usually adopted by healthcare systems. Indeed, recent research has shown that 66.2 % of the people in primary care in Ireland are living with MM. Health care utilisation and cost is significantly associated with MM, and additional chronic conditions lead to exponential increases in service usage and financial costs, and decreases in physical and mental well-being. Certain conditions, for example chronic pain, are highly correlated with MM. This study aims to assess the extent, profile, impact, and cost of MM among Irish adults with chronic pain.

Methods and analysis: Using cluster sampling, participants aged 18 and over will be recruited from Irish pain clinics and sent an information package and questionnaire asking them to participate in our study at three time points, 1 year apart. The questionnaire will include our specially developed checklist to assess the prevalence and impact of MM, along with validated measures of quality of life, pain, depression and anxiety, and illness perception. Economic data will also be collected, including direct and indirect costs.

Ethics and dissemination: Ethical approval has been granted by the Research Ethics Committee of the National University of Ireland, Galway. Dissemination of results will be via journal articles and conference presentations.

Main strength and weakness

Strength:

- The research study aims, to account for the prevalence and cost of multimorbidity in people living with chronic pain', are novel and would provide useful information for both the applied and research communities.

Weakness:

- Given the cohort of participants, the sample type, may arguably, be considered not entirely representative of all people living with chronic pain.

The guidelines for chronic disease management have traditionally taken a single disease approach,[1] which presents a challenge for patients who have multiple, sometimes discordant chronic conditions. As such, it has been argued that a single-morbidity approach in the context of multiple health conditions typically leads to inadequate disease management. [1] Thus, there has been a call for a more 'holistic' consideration of the patient and a disease management approach that focuses on *multimorbidity*.[1,2] Multimorbidity (MM) refers to the coexistence of two or more chronic conditions within one person, where no one condition takes precedence over another.[3] Despite the increasing interest of healthcare practitioners in the area of MM, Marengoni et al,[4] note that there remains "a remarkable gap between the harmful impact of multimorbidity at the individual and societal level and the amount of scientific and clinical research devoted to this topic" (p.435).

Prevalence of Multimorbidity

There are a variety of measures deployed to assess multimorbidity (e.g., Agborsangaya et al., 2012 [5]; Britt et al., 2008 [1]). Typically, however, prevalence research uses some form of checklist (i.e., lists of chronic conditions) to assess the prevalence of MM in a given population. Most of the prevalence literature and epidemiological work in the area of MM has come from research in Canada and Australia. Prevalence rates for these countries are 19% and 37.1% respectively [1,5] . However, epidemiological research has found pevalence estimates of MM ranging from 17% to over 90% internationally.[5] . In their Public Health Review, Boyd and Fortin [3] concluded that approximately one out of every four adults has two or more chronic conditions, and that half of all older adults globally have three or more chronic conditions.

From an Irish perspective, relatively little research on the prevalence of MM has been conducted; however, available figures show that between 27% [6] and 66.2% [7] of the population have two or more chronic conditions. While there is some uncertainty regarding the exact prevalence rates of MM, it is clear that MM is becoming increasingly more common.[5] Contributing factors to the increase in MM include, ageing populations, better medical treatments, lifestyle factors, and the increased prevalence of certain diseases in particular populations.[5, 8]

Impact of MM: challenges for patients and health practitioners

The occurrence of MM has significant social, psychological, economic, and physical implications for a person, creating a variety of management and treatment challenges. [3] For instance, different conditions require different and sometimes incompatible treatment solutions and as a result, multiple coexisting conditions can complicate medical treatment and affect long term recovery. Indeed, MM can contribute to a person becoming increasingly ill compared to another person with any one of the same index diseases but without MM, and it has also been linked to higher rates of postoperative complications.[9] Research on the impact of MM shows that it causes a decline in physical and mental functioning, is correlated with mental health issues, negatively influences quality of life, ability to work and employability, and is associated with increased mortality risk, as well as longer hospital stays and higher levels of health care usage.[3, 4, 9, 10]

MM and Chronic Pain

Chronic pain (CP) is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described by the patient in terms of such damage" that persists for a period in excess of 3 months. [11] CP is a major public health problem that can have debilitating physical, emotional, psychological, and financial consequences for those individuals living with it (see Azevedo, et al., 2012; Kroenke et al., 2013; Raftery et al., 2011). Prevalence estimates for CP vary across studies and countries; [12-16] one recent study found that 35.5% of the Irish population were living with CP. [14]

CP is highly correlated with MM, and is consistently identified as one of the most common conditions in those identified as having MM.[5] For example, in one Canadian study examining the prevalence of disease-combinations, sixteen common disease pairs were identified, with CP appearing in six of the combinations. Further, from the five most common disease triads identified in the same study, CP was involved in three of these combinations.[5] However, though the prevalence of CP is highly correlated with MM, little is known about the experience of chronic pain with other complex conditions. [17] To address this issue, Butchart et al (2009) examined the experience and management of chronic pain for people with other chronic conditions. The researchers found that patients with CP were more likely to report decreased health than for those without CP, and those with CP and comorbid heart failure or diabetes were less likely to be in employment.

Given the dearth of research examining the experience of MM were CP is a feature, as well as the high correlation and prevalence of CP and MM, it is important that research examines the prevalence and the relationship between the two more closely. While previous studies have examined the prevalence of MM in Irish samples, [7] no previous Irish study has examined the prevalence of MM in a population of people with CP.

Aims of the current research:

1. To determine the prevalence, impact, and cost of multimorbidity in a cohort of people in Ireland who live with chronic pain.
2. To identify the nature and profile of multimorbidity in which chronic pain is a central feature.
3. To develop a predictive model of multimorbid disability in a population of people with chronic pain.
4. To chart the developmental trajectory of multimorbidity in a sample of people with chronic pain.

Method

Design:

A prospective cohort study with three time points (1 year apart) assessing the prevalence of multimorbidity in a cohort of people with chronic pain will be employed.

Ethical Approval:

Ethical approval was granted by NUI Galway's Research Ethics Committee on 15 July 2015 (Reference number: 15/JULY/01).

Data Collection and Sample Size:

Inclusion criteria:

All participants of this study must be over 18 years of age and experiencing chronic non-cancer pain (according to the IASP definition). Individuals with terminal illness, severe mental illness or cognitive impairment that would prevent adequate understanding and participation in the study will be excluded.

Recruitment:

Recruitment will be carried out through Irish pain clinics. Staff in the pain clinics will inform patients of the study. Participants will be identified via the patient records from each of the 16 Pain Clinics in the Republic of Ireland; a list of patients who have visited each clinic over the previous 18 months will be requested. Each patient will be given an identifier by one of member of the research team (L'OC), and another member of the research team (SSH) will employ Stata 13.1 [18] to randomly select 150 participants from each clinic. These participants will be posted the survey packs containing the study information sheets, consent forms, multimorbidity checklist, and questionnaires by the research team. The participants will be directed to post their completed packs to the NUI Galway Centre for Pain Research using a stamped addressed envelope provided. In addition, the pack will contain a link to our website where the participants will able to complete the survey online should they prefer this method to the postal system.

Sample size:

Sample size was calculated using the equation proposed for prevalence research by Naing Winn and Rush (2006).[19] To calculate the sample size for a prevalence study, the expected prevalence is required. Based on previous research,[6, 7, 14, 20] the expected prevalence of MM in a population of people with CP is approximately between 22% and 54%. Nicholl [21] notes that if there is a doubt about the prevalence total in a given population, researchers should err toward assuming a 50% prevalence rate as it will yield a larger sample size. Therefore, using Naing et al's [19] equation and predicting that 50% of our sample may exhibit multimorbidity, confidence intervals set at .95, and the degree of precision (d) = .05 produced a sample size of 384. Using a predicted response rate of 40%, based on previous Irish prevalence research in the area of chronic pain, the sample size was calculated as 960. As we are sampling from Irish pain clinics, the design effect of using a cluster randomised trial must be taken into account, however, we were unable to identify a suitable intra-cluster correlation coefficient. Therefore, as demonstrated in a similar study on prevalence, [14] a median value of 0.01 was used. Adjusting for this, with an average of 150 patients per cluster, gives a design effect of 2.49 and a sample of 2391. A target sample of 2,400 will be recruited; 150 patients from each of the 16 Irish pain clinics.

Measures:

Sociodemographic and health information

Participants will be asked to supply details regarding age, gender, relationship status, highest educational attainment, occupational status (working full-time, working part-time, retired, unemployed, occupied with home duties, or other) and their occupation, to determine socioeconomic status (SES), as well as duration of chronic conditions, site(s) of chronic pain, and cause of chronic pain. Some details about previous and current medical and alternative treatments will also be collected.

Primary Measure:

The main focus of this study is to assess the point prevalence of multimorbidity in a cohort of people with chronic pain in Ireland. To that end, a specific disease count measure was developed.

Background to current MM Checklist

As Diederichs, Berger, and Bartels [10] highlight, there is no 'gold standard' measure of multimorbidity. Several measures of MM exist and have been developed for a variety of reasons, including different definitions of MM, different purposes for measuring MM, different required or available resources for data collection, and the type of data available.[7, 22] Moreover, there are no definitive criteria for the selection of chronic conditions that qualify for multimorbidity and therefore, no standardised list of the number and type of diseases to be included in a multimorbidity measure.[10] In a review of the literature, de Groot, Beckerman, Lankhorst, and Bauter [23] found that there were thirteen common measures of MM: twelve of these were disease indexes and one was a disease count.

Researchers that are interested in tallying the number of conditions that occur in patients as an outcome, or those examining the prevalence of MM, primarily use disease counts (e.g., Bayliss et al.[22]). To develop a disease count measure, researchers typically select and include the most common conditions found in the targeted population. For example, Bayliss, et al. [22] reviewed the literature and selected the 25 most common chronic conditions for a US sample to include in their measure. They developed a subjective scale or disease count, where participants marked which diseases they had and then rated them in terms of severity (i.e., how much each one affected their daily functioning).

Although different viewpoints exist regarding what conditions to include and how they should be selected for a MM disease count measure, guidelines [22, 24] have been

proposed to address these issues, which are based on work yielded from systematic reviews in the area.

Guidelines for developing an MM checklist

Fortin et al [24] proposed an operational definition of MM, whereby two or more diseases should be present in an individual and meet the diagnostic criteria for two separate areas of the Cumulative Illness Rating Scale (CIRS).[25] The CIRS is a measure that weights the severity of multimorbidity. It is divided into sections based on 14 different organ systems. These organ systems are as follows: 1. Cardiac, 2. Vascular, 3. Hematopoietic, 4. Respiratory, 5. Eyes, Ears, Nose, Throat and Larynx, 6. Upper GI, 7. Lower GI, 8. Hepatic, 9. Renal, 10. Genitourinary, 11. Musculoskeletal, 12. Neurological, 13. Endocrine/ Metabolic and Breast, and 14. Psychiatric. For a person to be considered to have a diagnosis of multimorbidity, chronic disease must be present in at least two different sections or organ systems. However, it is not necessary for a disease count to list either all conditions or all CIRS body systems. Fortin et al [26] recommend a minimum of seven conditions and argued that any list of conditions included in a MM prevalence study, should reflect the most common conditions in the population to be studied.

Process for developing the current MM checklist

In line with Fortin et al's [27] recommendations, the conditions included in the current disease count questionnaire were obtained from two large scale national reports on the Irish population more widely [26, 27] and four Irish research studies that had investigated the prevalence of multimorbidity and had compiled lists of conditions to examine.[6, 20, 27, 28] To ensure the list of conditions met international best practice recommendations, [22, 24] in terms of which conditions to include in an MM disease count list, we then combined our study with one international study that examined MM in people living with CP.[5] We also examined two of the most recent systematic reviews, which outline the most common conditions included in MM studies and contain recommendations for the type of conditions to be included in MM checklists.[10, 29] Following this, two health care practitioners were consulted and provided feedback, on which conditions to include, and one clinician, who is an expert in chronic pain, reviewed the entire MM checklist. From this review process, the three additional categories of conditions included were, as follows renal disorders, hepatic disorders, and headache disorders. Subsequently, we collapsed the conditions from this developmental process with respect to the CIRS organ system domains and removed any

duplicate conditions, leaving us a total of 34 conditions across 10 organ domains (see Table 1). We also added category options (e.g. "Other cardiac conditions") to ensure that useful data could be collected on conditions that didn't appear on the list, as well as a final "Any other condition not listed" category.

INSERT TABLE 1 HERE

Structure of MM checklist and operational definition of MM

Based on Fortin et al's [30] suggestion, a condition will be deemed suitable for inclusion as a multimorbidity when it meets one or both of the following criteria; a formal diagnosis has been provided by a doctor, and/ or a person is receiving prescribed medication for the particular condition. To ensure that participants understand what each condition is, a lay definition derived from a medical definition for each condition (see U.S. National Library of Medicine MeSH database [31]) will be provided (see Appendix A). Furthermore, similar to Bayliss et al,[22] who created a subjective survey disease count measure of MM, the current measure will include a rating scale (from 1 to 5; 1 being least impactful and 5 being most impactful) measuring the impact that each condition has on their daily functioning. The inclusion of this rating scale will enable the research to identify which chronic conditions have more of an impact on daily functioning and indeed, which disease combinations have more of a cumulative impact on daily functioning.

Secondary Measures

A number of secondary measures will be included to provide an accurate representation of the impact of MM and CP on participants. The measures outlined below were chosen to quantify the prevalence and impact of MM for people living with CP and were based on inclusion in previous chronic pain and multimorbidity prevalence research. [14]

Health Related Quality of Life

The Medical Outcomes Short Form-12 (SF-12) [32] will be used to assess health related quality of life. The SF-12 is a general measure of health-related quality of life that has been used and validated with European populations.[33] The SF-12 gathers information across 8 health domains; general health, physical functioning, emotional role limitation, physical role limitation, mental health, bodily pain, vitality, and social functioning. According to the norm-based method recommended by the test author, these items are scored to produce a Mental

Component Summary (MCS) and Physical Component Summary (PCS) of health-related quality of life.[32] Lower scores on either of these scales are indicative of a lower quality of life. Irish population norms are available [34] and will be used for comparison to the present sample. The SF-12 has been used as a measure of health related quality of life previously within chronic pain research and multimorbidity research. [21, 35, 36]

Depression and anxiety

Depression will be measured using the PHQ-9. The PHQ-9 is a widely used and well validated measure of depression [13] and it has been used with people living with chronic conditions. [37] The PHQ-9 contains 9 items that relate to the DSM IV criteria for depression. The items are scored on a 4 point Likert scale ranging from 0 "not at all" to 3 "nearly every day". The higher the score on the PHQ-9, the more symptom criteria a person meets. A cut-off score of above 10 indicates moderate depression and a score of above 15 indicates a clinical "case" of moderately severe depression.

Anxiety will be measured using the GAD-7. The GAD-7 is a validated and standardised measure of anxiety [38] and has been recommended for use in Chronic Pain studies.[39] The GAD-7 is a 7 item questionnaire that presents items relating to how often over the past couple of weeks a person has felt bothered by each of DSM IV symptom criteria for generalized anxiety disorder. Items are scored on a 4 point Likert scale ranging from 0 "not at all" to 3 "nearly every day". A higher overall score represents greater symptom severity.

Pain severity and disability

Pain related severity and disability will be measured by the Chronic Pain Grade Questionnaire, [40] commonly used in pain research. The Chronic Pain Grade Questionnaire categorises pain severity into one of four grades based on two dimensions; intensity and disability depending on pain experiences in the previous 3-6 months. It contains 7 items which can be completed by self-report, and includes questions both about the pain itself and its impact on daily functioning.

Pain intensity and interference

Intensity of pain and the degree of interference in the participant's life will be measured by the Brief Pain Inventory, specifically the short form of the tool. [41] This includes 9 items, to be completed by self-report, and asks about pain both now and over time. Two scores are

given: pain severity (out of 40) and pain interference (out of 70). Higher scores indicate greater pain severity and interference.

Multimorbidity Illness Perceptions Scale

The Multimorbidity Illness Perceptions Scale (MULTIPleS) [42] was developed to measure patient illness perceptions in the presence of multimorbidity. The MULTIPleS is a 22 item questionnaire. Each item has a Likert scale that runs from 0 to 3, where '0' indicates that a person 'strongly disagrees' with an item and '3' indicates that a person 'strongly agrees' with an item. Overall, the 22 items comprise five subscales; emotional representation, treatment burden, prioritising conditions, causal links, and activity limitations. The MULTIPleS is a relatively new scale so it has not yet been used as measure in clinical research. However, Gibbons et al [42] found that the scale provided a good fit to the Rasch model and demonstrated evidence of reliability and validity for each of the subscales.

Economic evaluation

The economic evaluation will be based on a number of questions relating to utilisation of healthcare services and financial costs to the participant (similar to Raftery, Ryan & Normand [43]). More specifically, we will examine costs that fall on the health and social care services by recording hospitalisations (frequency and duration), outpatient appointments, Accident and Emergency appointments, types and amounts of benefits received per month, community services used (e.g., GP and home help), and medication type, dosage, and frequency. These services/products will be translated into unit cost data for Ireland and provide an estimate of the cost of MM where CP is a feature for the health service. Furthermore, we will calculate indirect costs incurred personally by each individual with MM and their family. These will include expenditure for treatments and medications not paid for by the state, and the travel and wait time costs associated with availing of health services. Opportunity costs will also be calculated by quantifying work absenteeism or reduced employment due to MM. To generate this data, information on wages will be collected, however, should collecting this information not be possible, we will extrapolate income from age, education, and work type.

Risk of bias

To reduce the risk of participant selection bias one researcher will (LO'C) give each potential participant a unique identifier and another member of the research team (SSH) will use STATA 13.1 to randomly select participants. Furthermore, responders will be compared to

non-responders to assess and ensure there is no response bias between those that actively participate and those that do not,

Statistical Analyses

Graphical (e.g. box plots, labelled scatter-plots and case profiles plots) and numerical summaries (means, medians, standard deviations and interquartile ranges) will be provided for all variables. A chi-square (χ^2) test will be used to evaluate the relationship between gender and number of conditions. Odds Ratios will be calculated for risk factors of MM. Factors associated with MM will be analysed using univariate multiple regression and hierarchical regression will be employed to examine the relationships among the number and type of conditions and the outcome variables (i.e., depression, anxiety, QOL, illness perceptions, and severity of pain for example). All analyses will be conducted using SPSS version 22.

Data monitoring and management

This study will collect non-identifying, minimally invasive information and as such does not require a formal data monitoring committee. All information collected will be stored securely at the research site. Paper documents will be kept in locked cabinets, and electronic data will be stored on password-protected databases that can only be accessed by the research team.

Dissemination

Findings of the study will be disseminated in peer-reviewed publications following the data analysis. Researchers will also present the results at conferences. The research programme website will be regularly updated with news about the study to facilitate dissemination to the general public.

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Table 1: Source and Summary of Conditions included in the Multimorbidity Checklist

This table summarises the process of integrating previous multimorbidity studies and their listed conditions with the body system (CIRS domain) approach to develop the final list of conditions that appear in our multimorbidity tool (see the rightmost column). The asterisk denotes conditions included, as a result of advice from a healthcare practitioner.

CIRS Domain	Study and included conditions									**Included MM Checklist conditions**
	Teljeur et al 2013	Naughton et al 2006	Household Quarterly Report 2010	CARDI 2011/ Savva et al 2011 unpublished manuscript	TILDA 2011 Report: Fifty plus in Ireland	Diedrichs et al 2011 (systematic review)	Sinige et al 2013 (systematic review)	Agborsangaya et al 2012	Sinnott et al, 2015	
Cardiac	Heart disease	Hypertension/heart failure, Arrhythmias	Heart Attack, Heart Failure	Angina, Heart Attack	Cardiovascular disease (Angina, Heart attack, heart failure)	chronic ischemic heart disease, arrhythmia, insufficiency, infarction	Heart disease, heart failure, attack, angina (coronary artery disease)		Prior heart attack, angina, heart failure, aortic aneurysm, other cardiac disease, peripheral vascular disease,	**Angina, Arrhythmia, Heart Failure, Heart attack, other**
Vascular	hypertension	hypertension	Hypertension		hypertension	Hypertension	hypertension	Hypertension	Hypertension	**Hypertension**
Hematopoietic	High cholesterol, Hyperlipidaemia,	Hypercholesterolemia	High Cholesterol				Lipid metabolism disorders	High cholesterol		**High cholesterol**
Respiratory	Chest/lung disease, Asthma	Respiratory conditions		Asthma, COPD	Respiratory disease (e.g., bronchitis or emphysema)	COPD	COPD, Asthma		Asthma, bronchitis	**Asthma, Bronchitis, emphysema, COPD, other**
Eyes, ears, nose, throat and larynx		Glaucoma			Eye disease (e.g., glaucoma, age-related macular degeneration, cataracts)					**Glaucoma, other**
UPPER GI (esophagus, stomach, duodenum)							Gastrointestinal disease			**Gastrointestinal disease, Other GI conditions**
LOWER GI										

***Hepatic**										**Liver disease (e.g., Hepatitis)**
***Renal**										**Kidney disease (e.g., Chronic kidney disease)**
Genitourinary									Urinary incontinence	**Urinary incontinence, other**
Musculoskeletal	arthritis	Musculoskeletal conditions, Pagets/osteoporosis, Rheumatological conditions	Osteoporosis		Pain, arthritis, osteoporosis		Arthritis, osteoarthritis, osteoporosis, chronic back or neck disorder	Arthritis,	Chronic back pain, osteoarthritis, osteoporosis, rheumatoid arthritis	**Back pain or problem, neck pain or problem, osteoporosis, osteoarthritis, rheumatoid arthritis, other**
***Headache disorders**										**Headache disorder (e.g., Migraine, cluster headaches, tension headaches)**
Neurological		Parkinson's disease, dementia	Stroke	Stroke	Stroke/ TIA	Stroke	Dementia, cerebrovascular disease/ stroke		Stroke	**Stroke, TIA, Dementia, Other CNS conditions**
Endocrine/ metabolic and breast	Diabetes, hypothyroidism, obesity	Diabetes, thyroid disorders		Diabetes	Diabetes	Diabetes	Diabetes, Thyroid disease, obesity	Diabetes, obesity	Thyroid disease, diabetes	**Diabetes (Type 1), Diabetes (Type 2), Hypothyroidism, Obesity Other**
psychiatric	Depression	Psychiatric disorders, anxiety			Depression, anxiety	Depression	Depression	Depression/ anxiety	Anxiety, depression	**Depression, anxiety, other**
Other conditions:		Cancer		Cancer		Cancer	Cancer	Cancer	Cancer	**Any cancer in the past 5 years**
		Epilepsy, Gout, sleep disturbance						Sleep apnoea		**Epilepsy, Gout, Chronic sleep disturbance**

*CIRS = Cumulative Illness Rating Scale; MM = Multimorbidity

Author's contributions

BWS, LO'C, SH are involved in the design, delivery and evaluation of the trial and also drafted the manuscript. CPD, LC, JE and SO'H were involved in the editing of the manuscript and will be involved in the evaluation of the trial. BMcG contributed to the design of the intervention, supervises the study, and contributed to editing the manuscript.

Competing interests

The authors declare that they have no competing interests.

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Appendix A: Included conditions

The table below describes the conditions included in our study in more detail, using the MeSH descriptions for each condition for clarity. Each condition also lists a lay description, which will be used for greater clarity in the final questionnaire.

Condition	MeSH Description	Lay Description
Angina	The symptom of paroxysmal pain consequent to MYOCARDIAL ISCHEMIA usually of distinctive character, location and radiation. It is thought to be provoked by a transient stressful situation during which the oxygen requirements of the MYOCARDIUM exceed that supplied by the CORONARY CIRCULATION.	Angina is chest pain or discomfort where your heart muscle does not get enough blood, which may feel like pressure or a squeezing pain in your chest, indigestion, or pain in your shoulders, arms, neck, jaw or back. There are three types of angina: stable, unstable and variant.
Arrhythmia	Any disturbances of the normal rhythmic beating of the heart or MYOCARDIAL CONTRACTION. Cardiac arrhythmias can be classified by the abnormalities in HEART RATE, disorders of electrical impulse generation, or impulse conduction.	Cardiac arrhythmia, also known as cardiac dysrhythmia or irregular heartbeat, is a group of conditions where the heartbeat is irregular, too fast, or too slow.
Heart Failure	A heterogeneous condition in which the heart is unable to pump out sufficient blood to meet the metabolic need of the body.	A condition which occurs when the heart is unable to pump sufficiently to meet the body's needs.
Heart Attack	NECROSIS of the MYOCARDIUM caused by an obstruction of the blood supply to the heart (CORONARY CIRCULATION).	A heart attack occurs when blood stops flowing to part of the heart causing damage to the heart muscle. Also known as myocardial infarction (MI) or acute myocardial infarction (AMI),
Other Cardio	Aneurysm, atherosclerosis, peripheral artery disease, pericardial disease, cardiomyopathy or other	
Hypertension	Persistently high systemic arterial BLOOD PRESSURE. Based on multiple readings (BLOOD PRESSURE DETERMINATION), hypertension is currently defined as when SYSTOLIC PRESSURE is consistently greater than 140 mm Hg or when DIASTOLIC PRESSURE is consistently 90 mm Hg or more.	Blood pressure is the force of blood pushing against the walls of the arteries as the heart pumps blood. Hypertension or high blood pressure refers to this pressure rising and remaining high.
High Cholesterol	A condition with abnormally high levels of CHOLESTEROL in the blood. It is defined as a cholesterol value exceeding the 95th percentile for the population.	The presence of high levels of cholesterol in the blood (also called hypercholesterolemia or dyslipidaemia).
Hepatic conditions	Liver disease, cirrhosis, hepatitis, other liver conditions or other	
Asthma	A form of bronchial disorder with three distinct components: airway hyper-responsiveness (RESPIRATORY HYPERSENSITIVITY), airway INFLAMMATION, and intermittent AIRWAY OBSTRUCTION. It is characterized by spasmodic contraction of airway smooth muscle, WHEEZING, and dyspnea (DYSPNEA, PAROXYSMAL).	A common chronic disease of the airways which obstructs normal breathing with wheezing and coughing.
Bronchitis	A subcategory of CHRONIC OBSTRUCTIVE PULMONARY DISEASE. The disease is characterized by hypersecretion of mucus accompanied by a	Chronic bronchitis is defined as a cough that occurs every day with sputum production and that lasts for at least 3 months.

	chronic (more than 3 months in 2 consecutive years) productive cough. Infectious agents are a major cause of chronic bronchitis.	
Emphysema	Enlargement of air spaces distal to the TERMINAL BRONCHIOLES where gas-exchange normally takes place. Pulmonary emphysema can be classified by the location and distribution of the lesions.	An inflammatory response in the lungs resulting in narrowing of the small airways and breakdown of lung tissue
Chronic Obstructive Pulmonary Disease (COPD)	A disease of chronic diffuse irreversible airflow obstruction. Subcategories of COPD include CHRONIC BRONCHITIS and PULMONARY EMPHYSEMA. Enlargement of air spaces distal to the TERMINAL BRONCHIOLES where gas-exchange normally takes place. This is usually due to destruction of the alveolar wall. Pulmonary emphysema can be classified by the location and distribution of the lesions.	A type of obstructive lung disease characterized by chronically poor airflow
Other Respiratory	Pulmonary edema, embolism, obstructive sleep apnea, tuberculosis or other	
Glaucoma	An ocular disease, occurring in many forms, having as its primary characteristics an unstable or a sustained increase in the intraocular pressure which the eye cannot withstand without damage to its structure or impairment of its function.	A group of ocular (eye) disorders that result in optic nerve damage, often associated with increased fluid pressure in the eye
Other Eyes, Ears, Nose, and Throat	Hearing loss, tinnitus, meniere's disease, sinus conditions, obstructive sleep apnea, vocal cord disorders or other	
Gastrointestinal disease	Disease in any part of the GASTROINTESTINAL TRACT or the accessory organs (LIVER; BILIARY TRACT; PANCREAS).	Disease involving the gastrointestinal tract, namely the oesophagus, stomach, small intestine, large intestine and rectum, and the accessory organs of digestions, the liver (e.g., hepatitis), gallbladder, and pancreas (e.g., diabetes).
Other GI conditions	IBS, colitis, GERD or other	
Renal conditions	Kidney disease, renovascular disease, amyloidosis, lupus nephritis, or other	
Back Pain or Problem	Chronic pain located in the posterior regions of the THORAX; LUMBOSACRAL REGION; or the adjacent regions.	Pain felt in the back that usually originates from the muscles, nerves, bones, joints or other structures in the spine.
Neck pain or problem	Discomfort or more intense forms of pain that are localized to the cervical region. This term generally refers to pain in the posterior or lateral regions of the neck.	Pain felt in the neck
Other Pain Condition	Pain in any other location or a more general pain condition	
Osteoporosis	Reduction of bone mass without alteration in the composition of bone, leading to fractures. Primary osteoporosis can be of two major types: postmenopausal osteoporosis (OSTEOPOROSIS, POSTMENOPAUSAL) and age-related or senile osteoporosis.	A disease where decreased bone strength increases the risk of a broken bone
Osteoarthritis	A progressive, degenerative joint disease, the most common form of arthritis, especially in older persons.	Osteoarthritis (also known as degenerative arthritis, degenerative joint disease, or osteoarthrosis) is a type

		of joint disease that results from breakdown of joint cartilage and underlying bone
Rheumatoid arthritis	A chronic systemic disease, primarily of the joints, marked by inflammatory changes in the synovial membranes and articular structures, widespread fibrinoid degeneration of the collagen fibers in mesenchymal tissues, and by atrophy and rarefaction of bony structures.	A chronic, systemic inflammatory disorder that primarily affects joints
Other muskuloskeletal	Carpal tunnal syndrome, tendonitis, joint disorders, other bone/muscle/joint pain, repetitive strain injury or other	
Stroke	A group of pathological conditions characterized by sudden, non-convulsive loss of neurological function due to BRAIN ISCHEMIA or INTRACRANIAL HEMORRHAGES. Stroke is classified by the type of tissue NECROSIS, such as the anatomic location, vasculature involved, etiology, age of the affected individual, and hemorrhagic vs. non-hemorrhagic nature.	Stroke (also known as cerebrovascular accident (CVA), cerebrovascular insult (CVI), or brain attack) is when poor blood flow to the brain results in cell death. There are two main types of stroke: ischemic due to lack of blood flow and hemorrhagic due to bleeding.
TIA (Transient Ischaemic Attack)	Brief reversible episodes of focal, non-convulsive ischemic dysfunction of the brain having a duration of less than 24 hours, and usually less than one hour, caused by transient thrombotic or embolic blood vessel occlusion or stenosis	Often referred to as mini-strokes - A short, temporary episode of neurologic dysfunction caused by loss of blood flow.
Dementia	An acquired organic mental disorder with loss of intellectual abilities of sufficient severity to interfere with social or occupational functioning. The dysfunction is multifaceted and involves memory, behavior, personality, judgment, attention, spatial relations, language, abstract thought, and other executive functions. The intellectual decline is usually progressive, and initially spares the level of consciousness.	A broad category of brain diseases that cause a long term and often gradual decrease in the ability to think and remember such that a person's daily functioning is affected
Headache disorders	E.g. migraine, cluster headache, tension headaches	
Other CNS/Neuro conditions	Bell's palsy, dyskinesia, multiple sclerosis, motor speech disorders, Parkinson's, motor neurone disease or other	
Diabetes (Type 1),	A subtype of DIABETES MELLITUS that is characterized by INSULIN deficiency. It is manifested by the sudden onset of severe HYPERGLYCEMIA, rapid progression to DIABETIC KETOACIDOSIS, and DEATH unless treated with insulin. The disease may occur at any age, but is most common in childhood or adolescence.	Lack of insulin resulting from the autoimmune destruction of the insulin-producing cells in the pancreas which leads to increased blood and urine glucose, where administration of insulin is essential for survival
Diabetes (Type 2),	A subclass of DIABETES MELLITUS that is not INSULIN-responsive or dependent (NIDDM). It is characterized initially by INSULIN RESISTANCE and HYPERINSULINEMIA; and eventually by GLUCOSE INTOLERANCE; HYPERGLYCEMIA; and overt diabetes. Type II diabetes mellitus is no longer considered a disease exclusively found in adults. Patients seldom develop KETOSIS	A metabolic disorder that is characterized by high blood sugar in the context of insulin resistance and relative lack of insulin, initially managed by increasing exercise and dietary changes

	but often exhibit OBESITY.	
Hypothyroidism	A syndrome that results from abnormally low secretion of THYROID HORMONES from the THYROID GLAND, leading to a decrease in BASAL METABOLIC RATE.	A common endocrine disorder in which the thyroid gland does not produce enough thyroid hormone. It can cause a number of symptoms, such as tiredness, poor ability to tolerate cold, and weight gain
Other Endocrine/Metabolic	Cushing's syndrome, cystic fibrosis, hyperthyroidism, PCOS, or other	
Depression	An affective disorder manifested by either a dysphoric mood or loss of interest or pleasure in usual activities. The mood disturbance is prominent and relatively persistent.	Clinical depression (also known as major depressive disorder (MDD), major depression, unipolar depression, or unipolar disorder; or as recurrent depression in the case of repeated episodes) is a mental disorder characterized by a pervasive and persistent low mood that is accompanied by low self-esteem and by a loss of interest or pleasure in normally enjoyable activities
Anxiety	Persistent and disabling ANXIETY. - Feeling or emotion of dread, apprehension, and impending disaster	Anxiety disorders are a group of mental disorders characterized by feelings of anxiety and fear
Other psychiatric	Eating disorders, obsessive compulsive disorders, schizophrenia, bipolar disorder, pervasive developmental disorder, substance abuse or other	
Any cancer in the past 5 years	New abnormal growth of tissue. Malignant neoplasms show a greater degree of anaplasia and have the properties of invasion and metastasis, compared to benign neoplasms.	Cancer, also known as a malignant tumour or malignant neoplasm, is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body
Epilepsy	A disorder characterized by recurrent episodes of paroxysmal brain dysfunction due to a sudden, disorderly, and excessive neuronal discharge. Epilepsy classification systems are generally based upon: (1) clinical features of the seizure episodes (e.g., motor seizure), (2) etiology (e.g., post-traumatic), (3) anatomic site of seizure origin (e.g., frontal lobe seizure), (4) tendency to spread to other structures in the brain, and (5) temporal patterns (e.g., nocturnal epilepsy).	A group of neurological disorders characterized by epileptic seizures. Epileptic seizures are episodes that can vary from brief and nearly undetectable to long periods of vigorous shaking
Gout	Hereditary metabolic disorder characterized by recurrent acute arthritis, hyperuricemia and deposition of sodium urate in and around the joints, sometimes with formation of uric acid calculi.	Usually characterized by recurrent attacks of acute inflammatory arthritis—a red, tender, hot, swollen joint.
Genitourinary conditions	Urinary incontinence, urinary frequency, chronic UTI, or other	
Sleep Disorder	Conditions characterized by disturbances of usual sleep patterns or behaviors. Sleep disorders may be divided into three major categories: DYSSOMNIAS (i.e. disorders characterized by insomnia or hypersomnia), PARASOMNIAS (abnormal sleep behaviors), and sleep disorders secondary to medical or psychiatric disorders	Sleep disorders are broadly classified into dyssomnias, parasomnias, circadian rhythm sleep disorders involving the timing of sleep, and other disorders including ones caused by medical or psychological conditions and sleeping sickness.
Obesity	To be determined by calculating BMI	

Any other conditions	Please list any other conditions that affect you but do not appear on this list: